TIOTROPIUM RESPIMAT® IN CYSTIC FIBROSIS: PHASE 3 AND POOLED PHASE 2/3 RANDOMIZED TRIALS

Felix Ratjen [a,*], Paul Koker [b], David E. Geller [c,1], Berengere Langellier-Cocteaux [d], Florence Le Maulf [d], Sabine Kattenbeck [e], Petra Moroni-Zentgraf [f], J Stuart Elborn [g], on behalf of the Tiotropium Cystic Fibrosis Study Group

[a] Division of Respiratory Medicine, Department of Pediatrics, and Program in Physiology and Experimental Medicine, SickKids Research Institute, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada

[b] Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut, United States

[c†] Florida State University College of Medicine, Orlando, Florida, United States

[d] Boehringer Ingelheim France SAS, Reims, France

[e] Boehringer Ingelheim GmbH, Ingelheim, Germany

[f] Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim, Germany

[g] Centre for Infection and Immunity, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom

[1] Currently employed by AbbVie Inc., North Chicago, Illinois, United States

* Corresponding author at: The Hospital for Sick Children, 555 University Ave., Toronto, Ontario M5G 1X8, Canada. Tel: 416 813 6167; Fax: 416 813 6246; E-mail: felix.ratjen@sickkids.ca

Running title: Phase 3 trial of tiotropium Respimat® in CF

Abstract

Background: Tiotropium Respimat® improved lung function in a phase 2 trial in patients with cystic fibrosis (CF). We investigated its efficacy and safety in a phase 3 trial, including a pre-specified pooled analysis of the phase 2 and 3 trials.

Methods: 12-week, randomized, double-blind, placebo-controlled trial of tiotropium Respimat® 5 µg once daily in patients with CF (N=463).

Results: Co-primary efficacy endpoints showed no statistical difference between tiotropium and placebo: percent-predicted forced expiratory volume in 1 s (FEV_1) area under the curve from 0–4 hours ($AUC_{0–4h}$) (95% CI): 1.64% (0.27,3.55; p=0.092); percent-predicted trough FEV_1 (95% CI) 1.40% (0.50,3.30; p=0.15). Adverse events were similar in both groups. Pooled phase 2/3 trial results showed a treatment difference in favor of tiotropium: percent-predicted FEV_1 $AUC_{0–4h}$ (95% CI): 2.62% (1.34,3.90).

Conclusion: Tiotropium was well tolerated in patients with CF; lung function improvements compared to placebo were not statistically significant in the phase 3 trial.

Clinical trials

These studies are registered with clinical trial identifier numbers NCT00737100 and NCT01179347. These studies are also registered with the EudraCT number: 2008-001156-43 and 2010-019802-17.

Keywords: Bronchodilator, cystic fibrosis, Respimat, tiotropium

1. Introduction

Respiratory failure secondary to obstruction of pulmonary airways is the cause of death in more than 90% of people with cystic fibrosis (CF) [1]. Widely used therapy for CF patients includes antibiotics, airway clearance techniques and devices, pancreatic enzymes and nutritional supplements, as well as drugs such as dornase alfa, hypertonic saline, ibuprofen and inhaled bronchodilators [1]. No bronchodilator is currently approved for the treatment of CF, although their use is widespread. Several studies have provided evidence for efficacy of inhaled β2 adrenergic receptor agonists in people with CF, but the evidence is currently insufficient to recommend them for long-term care [2].

Tiotropium bromide is a once-daily, long-acting anticholinergic bronchodilator with the potential to improve lung function and alleviate symptoms in people with CF. Tiotropium can be delivered via Respimat® Soft Mist™ Inhaler (SMI), proven to be suitable even in children aged <5 years with a valved holding chamber (VHC), the AeroChamber Plus® with facemask [3,4]. In a phase 2 trial investigating two doses (2.5 and 5 µg once daily), tiotropium Respimat® dose-dependently improved lung function [5]. Based on the available efficacy, safety and pharmacokinetic data on the use of tiotropium in people with CF, the 5 µg dose was chosen for the current phase 3 study.

The objective of this phase 3 study was to determine the efficacy and safety of tiotropium Respimat® 5 µg versus placebo as add-on to usual maintenance therapy in people with CF. Based on the phase 2 trial results [5], we hypothesized that treatment with tiotropium for 12 weeks is more effective in improving lung function compared with placebo in people with CF of all ages.

2. Methods

2.1. Phase 3 trial

2.1.1. Study design

This 12-week multinational, multicenter, randomized, placebo-controlled, double-blind, parallel-group, phase 3 trial compared the efficacy and safety of tiotropium Respimat® (5 µg, two 2.5 µg puffs

once daily) with placebo. An open-label extension (12–60 weeks) assessed long-term safety and electrocardiogram (ECG) effects of tiotropium (Supplementary Fig. 1). Randomization was stratified by age group (Supplementary Fig. 2). The local institutional review board/independent ethics committee granted ethical approval. Written informed consent was obtained from each patient or the patient's legal representative. An external data safety monitoring board committee (associated with Cystic Fibrosis Foundation Therapeutics, Bethesda, Maryland, USA) monitored safety.

2.1.2. Participants

Inclusion and exclusion criteria are listed in full in the supplementary materials. Briefly, stable participants with a clear diagnosis of cystic fibrosis (children 5–11 years, adolescents ≥12 years and adults ≥18 years) were screened for pre-bronchodilator forced expiratory volume in 1 s (FEV_1) ≥25% of predicted values [6,7] (no upper limit). Children <5 years were included in the safety analyses only. Each patient was trained on the inhaler device using a placebo Respimat® (with VHC for patients <5 years). Usual CF maintenance therapy was continued during the study.

2.1.3. Endpoints

Co-primary endpoints were change from baseline (randomization) to 12 weeks in percent-predicted FEV_1 area under the curve from 0 to 4 h ($AUC_{0–4h}$), chosen as a more accurate representation of the response over time than individual time points, and trough FEV_1 percent-predicted. Secondary pulmonary endpoints were changes from baseline to 12 weeks in forced vital capacity (FVC) $AUC_{0–4h}$ percent-predicted, trough FVC percent-predicted and forced expiratory flow (FEF) between 25% and 75% of FVC ($FEF_{25–75}$) percent-predicted.

Additional secondary endpoints were change from baseline to 12 weeks in the revised CF questionnaire (CFQ-R) [8] and the proportion of patients with ≥1 pulmonary exacerbation during the double-blind treatment period as assessed by the Respiratory and Systemic Symptoms Questionnaire (RSSQ) method [9,10] after 12 weeks (further details in supplementary methods).

Safety and tolerability assessment was based on adverse event (AE) incidence, changes in vital signs, physical examination, clinical laboratory tests and ECG substudy results (supplementary methods).

2.1.4. Assessments

Pulmonary function tests (PFTs), FEV_1 and FVC were conducted according to American Thoracic Society/European Respiratory Society criteria [11] at screening visit (1 week before start of treatment); at weeks 1, 4 and 12 (double-blind part); at weeks 24–60 (open-label part); and at the end-of-treatment visit. At weeks 1 and 12 (day 85), PFTs were performed pre-dose (–10 min prior to study drug inhalation), at 30 min, and at 1, 2, 3 and 4 h after inhalation of study drug. At week 4 and weeks 24–60, PFTs were only carried out 30 min (±10 min) prior to drug administration. At the end of treatment, a single PFT was performed.

2.1.5. Statistical analyses

To assess efficacy, ≥360 patients were required to be randomized to tiotropium 5 µg or placebo in a 2:1 ratio. Primary analyses were performed in all treated patients who had ≥1 baseline PFT measurement and ≥1 post-baseline on-treatment PFT measurement. Change from baseline in the co-primary efficacy variables (FEV_1 $AUC_{0–4h}$ and trough FEV_1) and all secondary endpoints was analyzed using a restricted maximum likelihood–based mixed-effect model with repeated measures (MMRM). The MMRM included "treatment," "visit," "treatment-by-visit interaction" and "age group" (≤11, ≥12 years) as fixed categorical effects, and "baseline measurement" and "baseline-by-visit interaction" as continuous covariates. Unstructured (co)variance was used to model the within-patient errors. Superiority of treatment with tiotropium over placebo was tested at the α=0.025 (one-sided) level.

Sensitivity analyses to confirm the robustness of the primary results included MMRM analysis in liters, MMRM analysis with observed cases instead of imputed values (further details in the

supplementary material) and analysis of covariance (ANCOVA). For the co-primary endpoints, pre-specified subgroup analyses by age (≤11, ≥12 years) and concomitant long-acting β_2 agonist (LABA) use at baseline (yes/no) were performed. Treatment-by-subgroup interactions with interaction test p-values <0.1 were considered significant. For the analysis of the proportion of patients with ≥1 pulmonary exacerbation during the double-blind period (RSSQ), logistic regression with "treatment," "age group," "baseline weight" and "baseline predicted FEV_1" as covariates was used. For the CFQ-R, descriptive statistics were provided.

Safety endpoints were summarized descriptively. Blinding and randomization, sample size and handling of missing data are detailed in the supplementary methods. Analyses were implemented using Statistical Analysis System software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

2.2. Pre-specified pooling of phase 2 and 3 trials

The randomized, double-blind, 12-week clinical phase 2 [5] and 3 trials had identical design, outcome measures, and inclusion and exclusion criteria to enable pooling.

The primary analysis model for PFTs for the pooled analysis mirrored the analysis of the individual trials, with the addition of trial as a factor in the models. In addition to those pre-specified in the phase 2 and 3 trials, the following subgroups were pre-specified for the pooled analysis of the co-primary endpoints: baseline inhaled antibiotic use, asthma, screening lung function (<80%/≥80% predicted FEV_1) and sex. Safety and tolerability assessment was based on AE incidence in the pooled population.

3. Results

3.1. Phase 3 trial

The trial, conducted at 99 sites (20 countries) ran from November 11, 2010, to March 7, 2012. Patient disposition is summarized in Supplementary Fig. 3. In total, 464 people with CF were randomized and 463 received treatment (tiotropium, 308; placebo, 155). Mean (standard deviation; SD) age was 19.8 (12.5) years, ranging from 5 months (0.4 years) to 70.5 years. A total of 441 patients (95% of those treated) completed the double-blind treatment period and continued into the open-label active treatment phase. Overall, the demographic profile was balanced between the treatment groups and baseline characteristics were as expected for a study population with CF (Table 1).

Table 1. Patient demographics and characteristics of the study population at baseline.

	Main study (phase 3)		ECG substudy (phase 3)	Pooled phase 2/3 trials	
	Placebo	Tiotropium 5 µg	Tiotropium 5 µg	Placebo	Tiotropium 5 µg
No. of patients, n (%)	155 (100.0)	308 (100.0)	102 (100.0)	323	484
Sex					
Male, n (%)	90 (58.1)	169 (54.9)	63 (61.8)	186 (57.6)	263 (54.3)
Age, years (mean, SD)	20.6 (13.6)	19.3 (12.0)	22.5 (12.3)	20.5 (12.6)	19.8 (11.7)
Age group, n (%)					
≤11 years	55 (35.5)	110 (35.7)	24 (23.5)	99 (30.7)	162 (33.5)
≥12 years	100 (64.5)	198 (64.3)	78 (76.5)	224 (69.3)	322 (66.5)
<5 years[a]	8 (5.2)	15 (4.9)	1 (1.0)	8 (2.5)	15 (3.1)
5−11 years	47 (30.3)	95 (30.8)	23 (22.5)	91 (28.2)	147 (30.4)
12−17 years	28 (18.1)	60 (19.5)	18 (17.6)	63 (19.5)	84 (17.4)
≥18 years	72 (46.5)	138 (44.8)	60 (58.8)	161 (49.8)	238 (49.2)
Percent-predicted FEV_1, (mean, SD)	77.5 (24.4)	76·1 (22·5)		77.0 (24.0)	76.0 (25)
≤11 years	90.6 (19.6)	89.8 (17.8)		90.1 (19.5)	88.8 (16.8)
≥12 years	71.3 (24.0)	69.4 (21.5)		70.1 (23.5)	69.1 (21.8)
BMI, kg/m^2 (mean, SD)	19.61 (3.59)	19.48 (3.99)	19.99 (3.29)	20.0 (4.1)	19.7 (4.0)
Baseline concomitant medications, n (%)	155 (100.0)	308 (100.0)	88 (86.3)		
Inhaled antibiotics	74 (47.7)	113 (36.7)	40 (39.2)	136 (42.1)	168 (34.7)
SABA	80 (51.6)	150 (48.7)	46 (45.1)	182 (56.3)	260 (53.7)
ICS	67 (43.2)	138 (44.8)	38 (37.3)	150 (46·4)	214 (44.2)
LABA	57 (36.8)	115 (37.3)	34 (33.3)	123 (38.1)	173 (35.7)

[a] Participants <5 years were only included in safety analyses (no pulmonary function tests).

BMI: body mass index; ECG: electrocardiogram; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; SABA: short-acting β_2 agonist; SD: standard deviation.

3.1.1. Co-primary efficacy endpoints

There was no statistical difference between tiotropium and placebo for either co-primary efficacy endpoint (Fig. 1A; tables 2 and 3; change from baseline difference of tiotropium versus placebo in percent-predicted FEV_1 $AUC_{0–4h}$: 1.64%; 95% confidence interval [CI] –0.27 to 3.55; p=0.092, and percent-predicted trough FEV_1: 1.40%; 95% CI –0.50 to 3.30; p=0.15).

The results of the primary analyses were supported by the results of sensitivity analyses based on analyses in liters (tables 2 and 3), ANCOVAs and observed case analyses (Supplementary Table 1).

Assessment by age showed a greater difference in FEV_1 $AUC_{0–4h}$ (percent-predicted) between tiotropium and placebo in patients aged ≥12 years (2.58%, 95% CI 0.50 to 4.65) than ≤11 years (–0.63%; 95% CI –4.58 to 3.32). An improvement in lung function with placebo was observed, driven by results from patients aged ≤11 years (tables 2 and 3).

The difference between tiotropium and placebo for the change in percent-predicted FEV_1 $AUC_{0–4h}$ was greater for patients taking concomitant LABA at baseline (3.40%, 95% CI 1.50 to 5.30) than not (1.80%, 95% CI 0.38 to 3.21). This was also true for patients with a screening FEV_1 of <80% (3.00%, 95% CI 1.40 to 4.60) compared with those patients with a screening FEV_1 of ≥80% (1.11%, 95% CI –0.52 to 2.74).

Table 2. Adjusted mean (SE) changes in FEV_1 $AUC_{0–4h}$ (percent-predicted) overall—phase 3 trial and pooled phase 2 and 3 trial*, and in patients aged ≤11 years and ≥12 years treated with tiotropium 5 µg or placebo after 12 weeks[a]—phase 3 trial.

		Change from baseline	Treatment effect		
Treatment	N[b]	Mean[c] (SE)	Mean[c] (SE)	95% CI	p-Value
Phase 3 trial: Overall, percent -predicted					
Placebo	146	0.87 (0.80)			
Tiotropium 5 µg	292	2.51 (0.57)	1.64 (0.97)	–0.27 to 3.55	0.092
Phase 3 trial: Overall, L					
Placebo	146	–0.011 (0.022)			
Tiotropium 5 µg	292	0.059 (0.027)	0.070 (0.027)	0.017 to 0.124	0.010
Pooled phase 2 and 3: Overall, percent-predicted					
Placebo	315	–0.42 (0.51)			
Tiotropium 5 µg	469	2.20 (0.42)	2.62 (0.65)	1.34 to 3.90	<0.001
					p value of treatment-by-age interaction
Phase 3 trial: ≤11 years, percent-predicted					
Placebo	47	3.96 (1.64)			
Tiotropium 5 µg	94	3.33 (1.14)	–0.63 (2.00)	–4.58 to 3.32	
Phase 3 trial: ≥12 years, percent-predicted					0.26
Placebo	100	–0.71 (0.86)			
Tiotropium 5 µg	198	1.86 (0.61)	2.58 (1.05)	0.50 to 4.65	

[a] Analysis of the FAS study population based on MMRM model. Analysis with imputation on the FAS. Baseline is pre-dose measurement on day 1.

[b] This N refers to the number of patients in the FAS.

[c] Based on MMRM, with fixed effects of trial (pooled analysis only), treatment, visit, treatment-by-visit interaction, age group (≤11, ≥12 years), baseline, baseline-by-visit interaction (and random effect of center for study 205·339 only). Within-patient errors are modeled by unstructured (co)variance matrix.

AUC_{0-4h}: area under the curve from 0 to 4 h; CI: confidence interval; FAS: full analysis set; FEV_1: forced expiratory volume in 1 s; MMRM: mixed-effect model with repeated measures; SE: standard error.

Table 3. Adjusted mean (SE) changes in trough FEV_1 response overall —phase 3 trial and pooled phase 2 and 3 trial*, and in patients aged ≤11 years and ≥12 years treated with tiotropium 5 µg compared with placebo after 12 weeks[a]—phase 3 trial.

		Change from baseline	Treatment effect		
Treatment	N[b]	Mean[c] (SE)	Mean[c] (SE)	95% CI	p-Value
Phase 3 trial: Overall, percent-predicted					
Placebo	147	0.72 (0.80)			
Tiotropium 5 µg	293	2.12 (0.58)	1.40 (0.97)	–0.50 to 3.30	0.15
Phase 3 trial: Overall, L					
Placebo	144	–0.024 (0.022)			
Tiotropium 5 µg	287	0.043 (0.016)	0.067 (0.027)	0.015 to 0.119	0.012
Pooled phase 2 and 3: Overall, percent-predicted					
Placebo	315	–0.34 (0.54)			
Tiotropium 5 µg	469	1.51 (0.45)	1.85 (0.68)	0.53 to 3.18	0.006
					p-value of treatment-by-age interaction
Phase 3 trial: ≤11 years, percent-predicted					
Placebo	46	4.06 (1.64)			
Tiotropium 5 µg	94	2.81 (1.14)	–1.24 (2.00)	–5.20 to 2.71	
Phase 3 trial: ≥12 years, percent-predicted					0.052
Placebo	98	–1.29 (0.85)			
Tiotropium 5 µg	193	1.27 (0.61)	2.56 (1.05)	0.49 to 4.62	

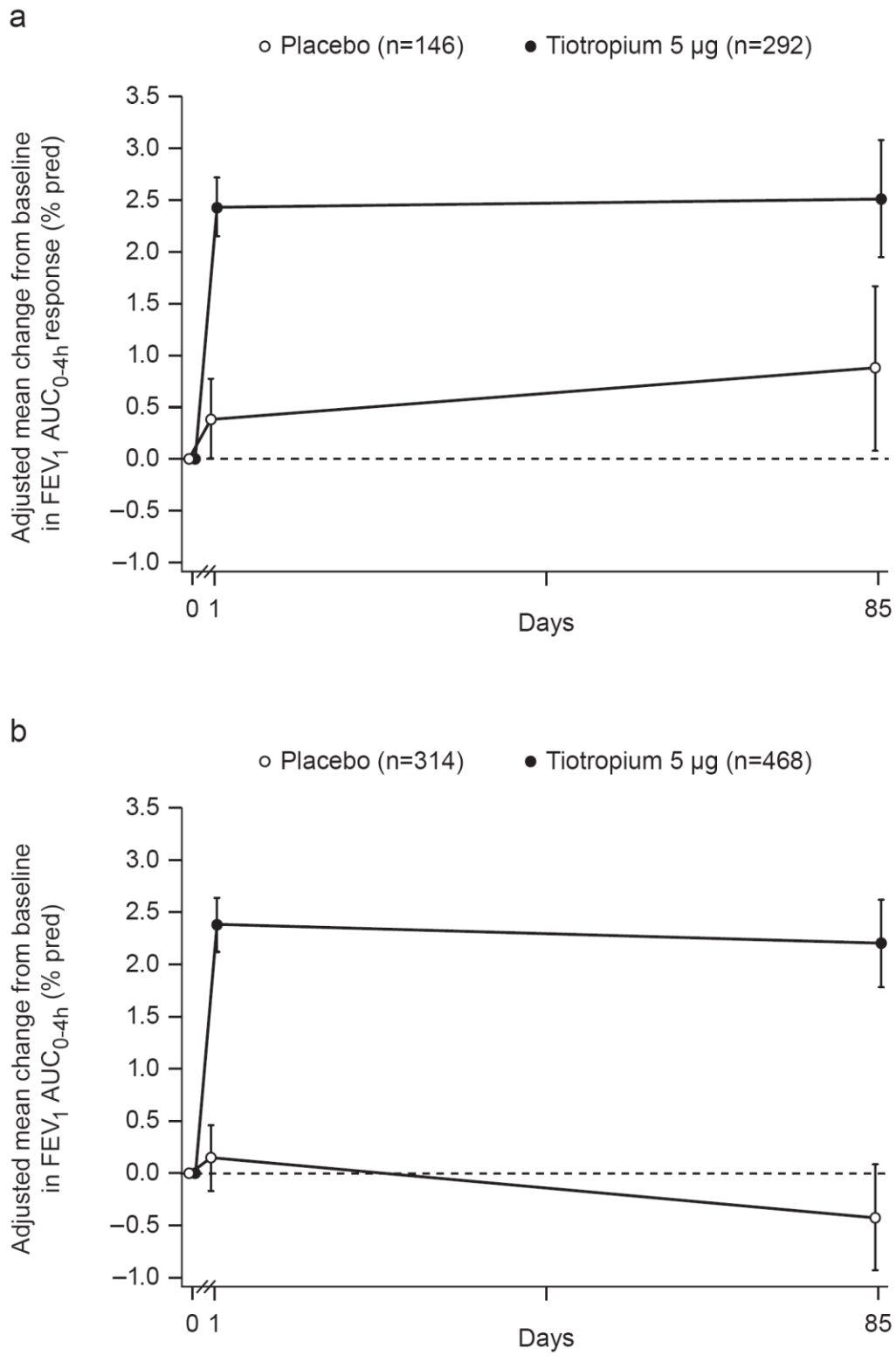
[a] Analysis of the FAS study group based on MMRM model. Analysis with imputation on the FAS. Baseline is pre-dose measurement on day 1.

[b] This N refers to the number of patients in the FAS.

[c] Based on MMRM, with fixed effects of trial (pooled analysis only), treatment, visit, treatment-by-visit interaction, age-group (≤11, ≥12 years), baseline, baseline-by-visit interaction (and random effect of center for study 205·339 only). Within-patient errors are modeled by unstructured (co)variance matrix.

CI: confidence interval; FAS: full analysis set; FEV_1: forced expiratory volume in 1 s; MMRM: mixed-effect model with repeated measures; SE: standard error.

Fig. 1. Adjusted mean FEV_1 $AUC_{0–4h}$ (percent-predicted ± SE) change from baseline by weeks (FAS). A. phase 3 trial; B. pooled phase 2 and 3 trials. $AUC_{0–4h}$, area under the curve from 0 to 4 h; FAS: full analysis set; FEV_1: forced expiratory volume in 1 s; SE: standard error.



3.1.2. Other lung function measures

Secondary spirometry endpoints results followed those for co-primary endpoints: tiotropium and placebo differences in FVC AUC_{0-4h} change from baseline in percent-predicted, 1.09% (95% CI –0.68 to 2.86; p=0.23), trough FVC, 1.20% (95% CI –0.62 to 3.02; p=0.19) and FEF_{25-75}, 0.86% (95% CI –2.59 to 4.32; p=0.62).

3.1.3. Pulmonary exacerbations and quality of life

Nine percent of patients taking tiotropium and 8% of patients receiving placebo reported ≥1 pulmonary exacerbation during the double-blind period (RSSQ method); tiotropium versus placebo odds ratio [OR] 1.092; 95% CI 0.453 to 2.633; p=0.84. No relevant differences were noted between the treatment groups in mean changes from baseline to 12 weeks in CFQ-R domain scores (data not shown).

3.1.4. Safety

During the double-blind period of this study, AEs were reported at a similar frequency in the tiotropium and placebo groups (tiotropium, 65%; placebo, 68%; Table 4). The most frequently reported AEs were in the system organ classes (SOCs) of infections and infestations and respiratory, thoracic and mediastinal disorders, with cough being the most frequently reported AE (tiotropium, 18%; placebo, 13%; Supplementary Table 2). Drug-related AEs were balanced between treatment groups. Serious AEs (SAEs) were reported at a higher frequency in the tiotropium group (tiotropium, 12%, placebo, 8%). The treatment difference was driven partly by a greater proportion of AEs in the infections and infestations SOC (in particular pneumonia) and by a slightly higher percentage of individuals with pulmonary exacerbation in the tiotropium group.

No unexpected findings were noted in the results from the open-label treatment period, the entire main period and the ECG study (Supplementary Table 3).

Table 4. Overall summary of adverse events (treated set)—phase 3 trial.

	Double-blind period		Open-label treatment period	Entire main study	ECG substudy
	Placebo	Tiotropium 5 µg	Switched to tiotropium 5 µg	Tiotropium 5 µg	Tiotropium 5 µg
No. of patients, n (%)	155 (100.0)	308 (100.0)	147 (100.0)	308 (100.0)	102 (100.0)
Patients with any AE, n (%)	105 (67.7)	200 (64.9)	112 (76.2)	256 (83.1)	53 (52.0)
Patients with severe AE, n (%)	5 (3.2)	15 (4.9)	10 (6.8)	29 (9.4)	3 (2.9)
Patients with a study drug-related AE[a], n (%)	11 (7.1)	27 (8.8)	10 (6.8)	35 (11.4)	4 (3.9)
Patients with other significant AE[b], n (%)	3 (1.9)	8 (2.6)	4 (2.7)	12 (3.9)	0 (0.0)
Patients with AE leading to discontinuation of study drug, n (%)	3 (1.9)	8 (2.6)	5 (3.4)	15 (4.9)	0 (0.0)
Patients with serious AEs, n (%)	13 (8.4)	36 (11.7)	24 (16.3)	62 (20.1)	6 (5.9)
Fatal, n	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immediately life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Required hospitalization	13 (8.4)	36 (11.7)	24 (16.3)	61 (19.8)	6 (5.9)
Prolonged hospitalization	1 (0.6)	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)

Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0·0)	0 (0.0)	1 (0.7)	1 (0.3)	0 (0.0)

[a] As assessed by the study investigators.

[b] As defined by International Conference on Harmonisation E3 guidelines. A patient may have been counted in more than one seriousness criterion.

AE: adverse event; ECG: electrocardiogram.

3.2. Pre-specified pooled phase 2 and phase 3 study results

Of the 808 patients randomized to tiotropium 5 µg or placebo in the two trials, 807 were included in the treated set of the pooled analysis, with an approximate 1:2 ratio of patients aged ≤11 years and patients aged ≥12 years (546 patients, 68%). The characteristics of people with CF were comparable between the two trials (including mean [SD] age 20.3 [12.1] years, range 0.4–69.7) and well balanced between treatment groups (Table 1).

A difference of 2.62% (95% CI 1.34 to 3.90) in favor of tiotropium was observed in the change from baseline in percent-predicted FEV_1 $AUC_{0–4h}$ and of 1.85% (95% CI 0.53 to 3.18) in percent-predicted trough FEV_1 (Fig. 1B, tables 2 and 3). There was also a difference in favor of tiotropium for the adjusted mean changes from baseline to week 12 in FEV_1 $AUC_{0–4h}$ in liters (0.085 L; 95% CI 0.050 to 0.121) and in trough FEV_1 (0.064 L; 95% CI 0.028 to 0.100). There were also positive differences in FEV_1 $AUC_{0–4h}$ (adjusted means between 1.43–4.65% predicted) in favor of tiotropium 5 µg across all subgroups assessed (age, sex, screening lung function, baseline use of LABA, inhaled antibiotics and asthma at baseline), although children aged ≤11 years, patients with a FEV_1 ≥80% and those not taking LABA at baseline seem to derive less benefit from tiotropium treatment (Supplementary Fig. 4). The unadjusted mean changes from baseline to week 12 for percent predicted FEV_1 $AUC_{0–4h}$ in patients aged 12 to 17 years and ≥18 years are consistent with those observed for MMRM analysis for the ≥12 year subgroup (placebo: -1.58% change from baseline, 95% CI: -2.61 to -0.56; tiotropium 5µg: 1.41% change from baseline, 95% CI: 0.54 to 2.27; treatment difference: 2.99%, 95% CI: 1.65 to 4.33), which provides support for using the combined group (≥12 year subgroup) as a representation of what occurs in patients aged 12 to 17 years and ≥18 years separately.

A similar proportion of patients in the tiotropium and placebo groups experienced pulmonary exacerbations, as assessed by the RSSQ (7.5% versus 8.6%; OR 0.82; 95% CI 0.46 to 1.48). Baseline CFQ-R scores were 73 for placebo and 72 for tiotropium. Mean changes in CFQ-R scores from baseline to day 85 were 0.6 and –1.5, respectively, for all questionnaires combined. While baseline

scores were relatively high, changes within each treatment group were small and no difference between treatments was observed. The most frequently reported AEs were of respiratory nature. A >2-fold increase compared with placebo was observed in patients taking tiotropium for AEs of nasal congestion and productive cough, particularly for those aged ≤11years (Supplementary tables 4 and 5); however none were reported as SAEs or led to treatment discontinuation. A slightly higher incidence of AEs relating to pulmonary exacerbations was observed in patients taking tiotropium versus placebo (Supplementary Table 6). In the pooled analysis, the safety and tolerability of tiotropium were comparable overall with placebo (supplementary results).

4. Discussion

In the phase 3 trial, tiotropium was associated with small improvements in spirometry endpoints, but statistical significance versus placebo was not reached. A pre-specified pooling of the phase 2 and 3 trials was performed to enhance the precision of estimates and to evaluate the effects in various subgroups of interest; both co-primary endpoints demonstrated improvements in lung function with tiotropium versus placebo. No effect was seen in pulmonary exacerbation rates or respiratory symptoms quantified by CFQ-R.

The difference in outcomes from the phase 2 [5] and 3 trials were largely driven by the ≤11-year age group, though the reasons for this are not clear. The high frequency of patients with >80% FEV_1 predicted at screening in this age group may have reduced the chances of improvements in lung function. However, in the phase 3 trial, patients ≤11years in the placebo group showed an improvement in percent-predicted FEV_1 $AUC_{0–4h}$ over time, which suggests a learning effect during the trial among the younger patients, who were less skilled in performing spirometry. In a recent study of inhaled mannitol, a sustained, significant ($p<0.001$) improvement in FEV_1 was seen in the control group [12], but the improvement was not significant in another similarly designed study ($p=0.059$) in similar populations [13]. Interestingly, in the pooled analysis, significant improvements in the mannitol versus control group in FEV_1 occurred in patients aged ≥18 years old but not in younger

participants [14]. Furthermore, and similar to the current study, improvements in percent-predicted FEV_1 were observed in the placebo group in the 6–17-year age group [14], raising the question of whether more intense pulmonary function testing should be done as a run-in phase in children and adolescents (≤18 years) with CF.

The trial included people with CF of all ages (5 months to 70.5 years) and disease severities; it can therefore be considered of clinical relevance. Overall, the broad inclusion criteria for the tiotropium trials in CF facilitated patient recruitment but may have limited the chance of showing efficacy in improving pulmonary function and symptoms. Subgroup analyses suggest that adolescents and adults with CF, those with lower FEV_1 and those taking concomitant LABA were more likely to achieve greater benefit from long-term treatment with tiotropium.

People with CF use complex and intense medication regimens. In this study, tiotropium was tested on top of usual CF maintenance therapy, including bronchodilators such as short-acting β_2 agonists, LABAs and LABA/inhaled corticosteroid combinations, antibiotics, inhaled antibiotics and mucolytics. The magnitude of improvement in pulmonary function in percent-predicted FEV_1 $AUC_{0–4h}$ observed with tiotropium in people with CF (pooled phase 2/3: 2.62%) was relatively small. It is difficult to compare results with those published in the literature since results are presented in terms of relative rather than absolute differences and sometimes with absolute changes in lung volume data rather than percent-predicted data. In two recent identical trials of mannitol in CF in which FEV_1 was expressed in the same way as in our trial (difference versus placebo in percent-predicted FEV_1 was 2.4%, 95% CI 0.9 to 3.9 in one trial [12] and 1.9%, 95% CI –0.02 to 3.8 in the other), changes were similar in magnitude to those demonstrated for tiotropium [13]. Treatment differences must also be considered in light of the study design and short duration of the trials. Patients were already on usual standard of care maintenance therapy and no upper limit of percent-predicted FEV_1 at baseline was set as a criterion for study entry, limiting the room for improvement.

The numerical, but not statistically significant, increase in infections reported as AEs seen in the phase 3 study was not observed in the phase 2 study; in the pooled analysis, incidence of all AEs in the SOC infections favored placebo, whereas SAEs favored tiotropium. Collectively, safety and tolerability were comparable between tiotropium and placebo.

5. Conclusion

Efficacy, based on lung function and RSSQ results, of inhaled tiotropium delivered by the Respimat® SMI in people with CF as add-on to usual CF maintenance therapy was not established in this phase 3 trial. In the pooled phase 2 and 3 results, the improvements in lung function with tiotropium were not accompanied by clinical effects on the frequency of pulmonary exacerbations or quality of life. Subgroup analyses using pooled phase 2 and 3 results suggest that some individuals with CF may derive clinical benefit from tiotropium. Tiotropium Respimat® 5 µg was well tolerated in people with CF and the overall safety profile was consistent with that of tiotropium in chronic obstructive pulmonary disease.

Acknowledgments

Writing and editorial assistance was provided by Elena Garonna and Sarah J Petit of PAREXEL, who were contracted by Boehringer Ingelheim for these services.

Financial support

Funding was provided by Boehringer Ingelheim. Boehringer Ingelheim was involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Author contributions

All authors were involved in planning and conducting the study and analyzing and reporting of the results. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, were fully responsible for all content and editorial decisions and were involved at all stages of manuscript development. The authors received no compensation related to the development of the manuscript. The corresponding author, Felix Ratjen, is responsible for the overall content as guarantor.

Conflict of interest disclosures

FR acts as a consultant for Boehringer Ingelheim and is the principal investigator for this study; DEG declares no conflicts related to bronchodilators in cystic fibrosis, and is currently employed by AbbVie Inc.; JSE acts as a consultant for Boehringer Ingelheim and was principal investigator for the phase 2 study. PK, BLC, FLM, SK and PMZ are employees of Boehringer Ingelheim.

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